

What are good drug targets and how to find them?

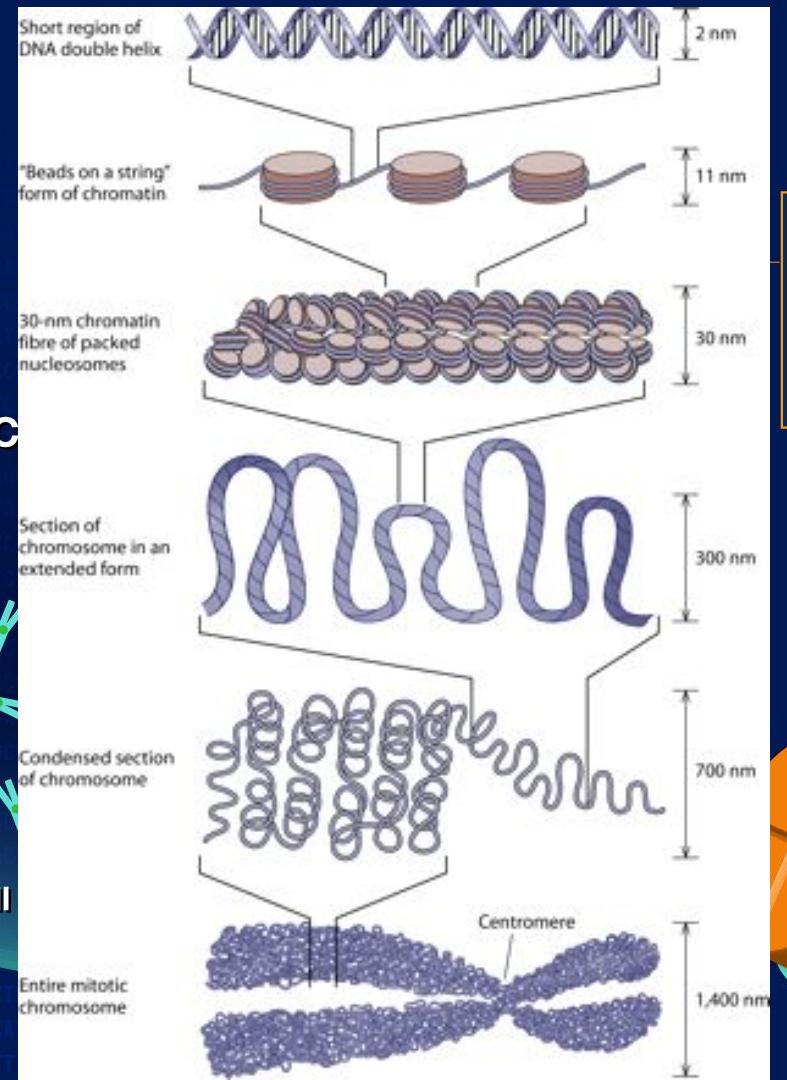
*Mathematical and Computational Biology in Drug
Discovery (MCBDD), Module I*

Dr. Jitao David Zhang, March 2021

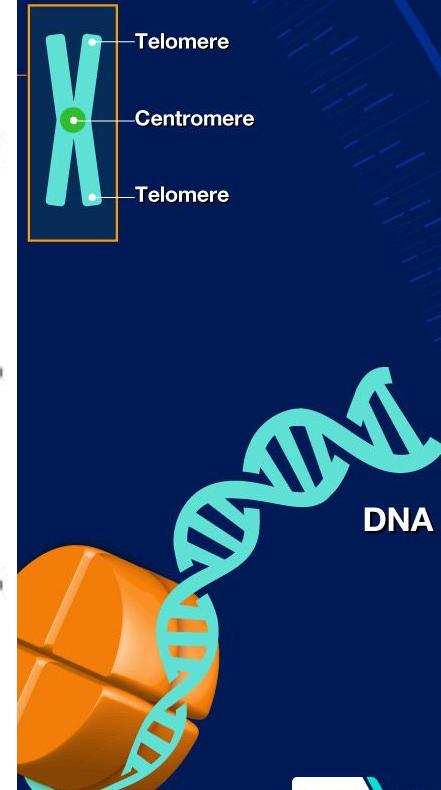
Q&A

- **Can genetics explain differences of numbers of infection and death caused by SARS-CoV-2 between countries?**
- **How much does genotyping cost? If we sequence each individual on the planet, do we solve the problem of target identification and drug discovery?**
- **Why we are so bad at selecting drug targets? Any hope that we can do it better?**
- **Any more questions?**

Chromosome

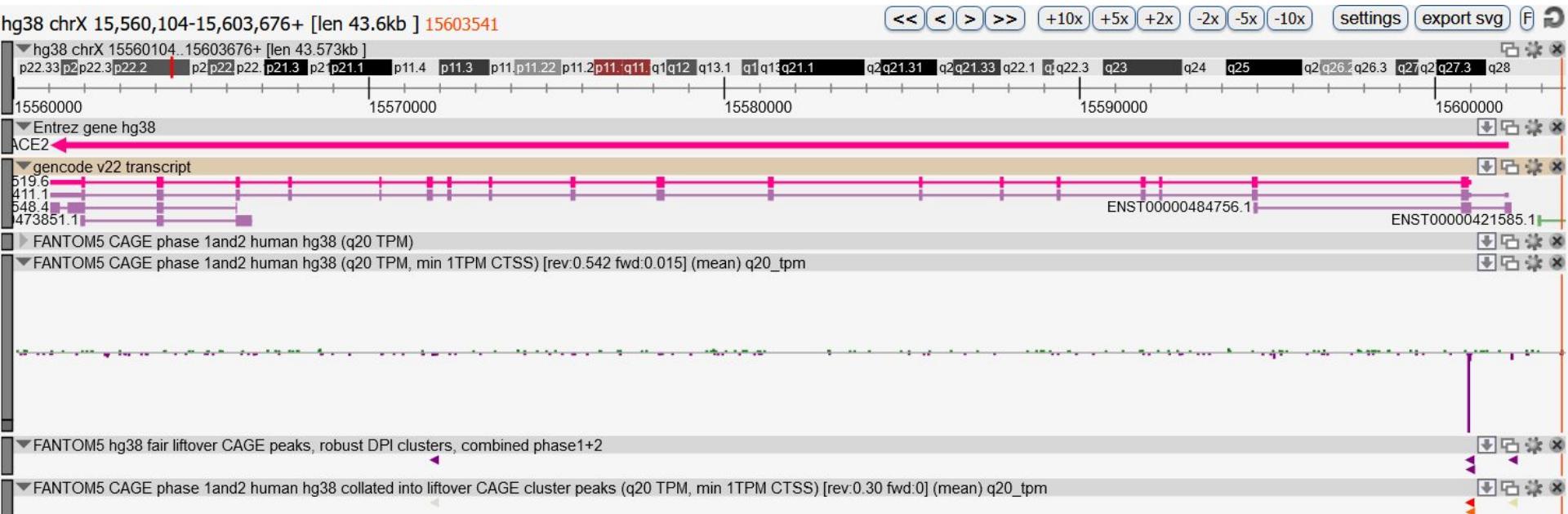


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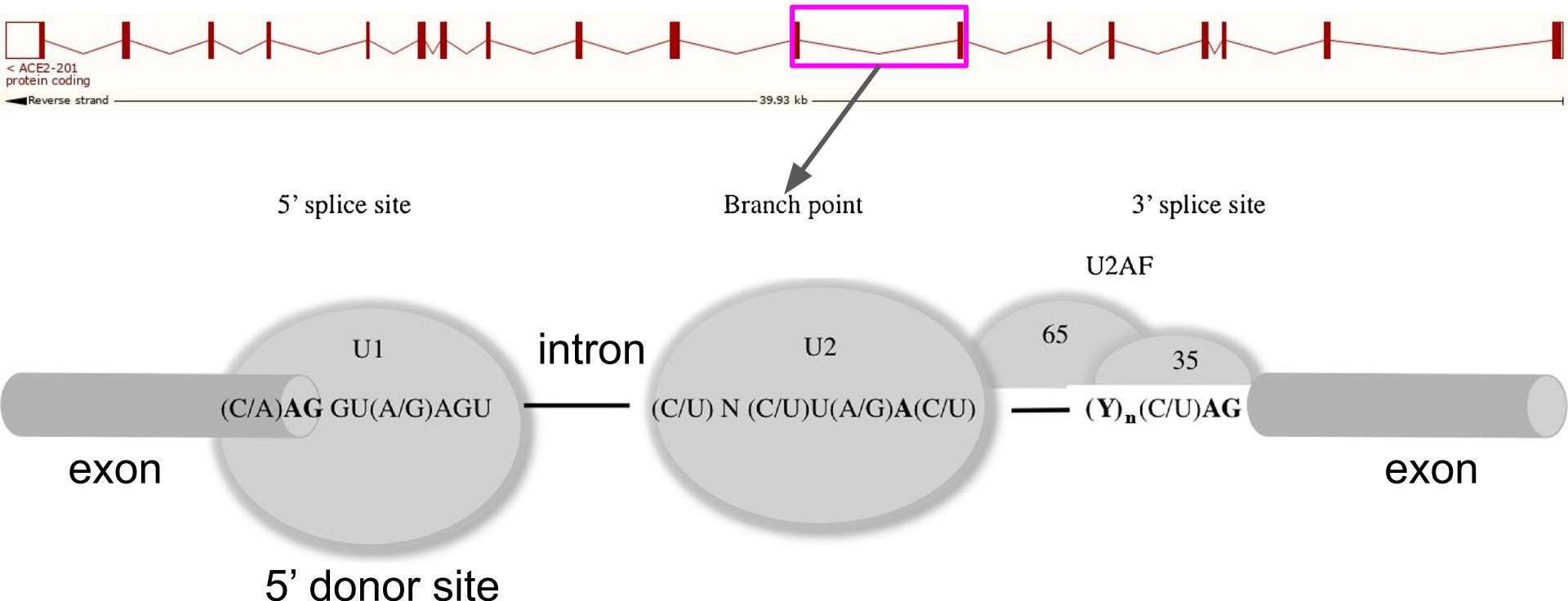
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Gene structure and gene expression



ACE2 viewed in **FANTOM5/ZENBU**

The splicing code



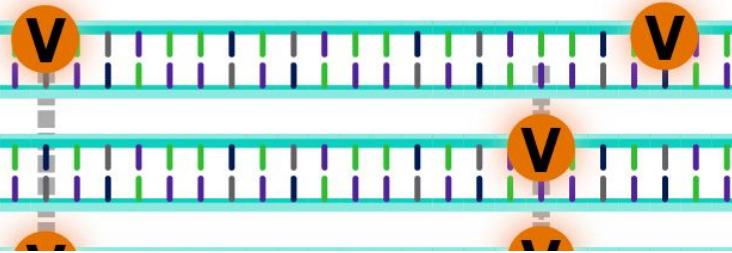
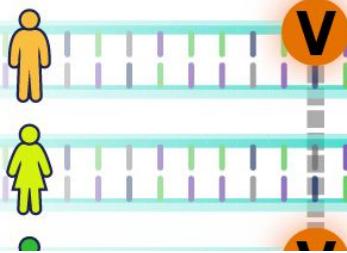


Person one

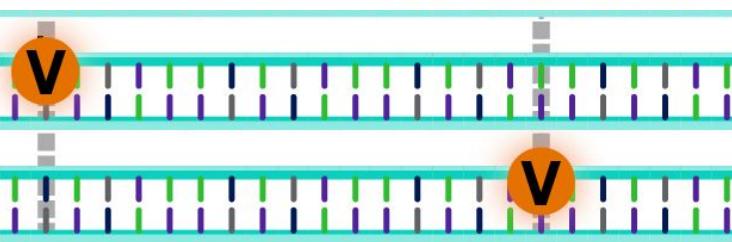
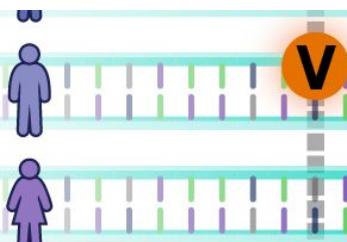
A G A C G C T

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count
17-7579017-C-T	E	c.74+22G>A	● intron		Likely benign		1
17-7579831-C-T	E	c.74+8G>A	● splice region		Likely benign		1
17-7579924-G-A	E G	c.-12C>T	● 5' UTR		Likely benign		7
17-7579932-G-C	E	c.-20C>G	● 5' UTR		Likely benign		2
17-7578142-C-A	E G	c.672+35G>T	● intron		not provided		9
17-7577142-C-A	E	p.Gly266Ter	● stop gained		Pathogenic		1
17-7578188-C-A	E	p.Glu221Ter	● stop gained		Pathogenic		1
17-7578263-G-A	E	p.Arg196Ter	● stop gained		Pathogenic		1
17-7576928-TAGGAA...	E	c.920-14_920-3delTGC...	● splice region		Uncertain significance		2
17-7578171-C-A	E G	c.672+6G>T	● splice region		Uncertain significance		2
17-7578171-C-T	E	c.672+6G>A	● splice region		Uncertain significance		1
17-7579934-C-T	G	c.-22G>A	● 5' UTR		Uncertain significance		1
17-7565206-T-A	G	c.*51A>T †	● 3' UTR				1
17-7565222-C-T	G	c.*35G>A †	● 3' UTR				1

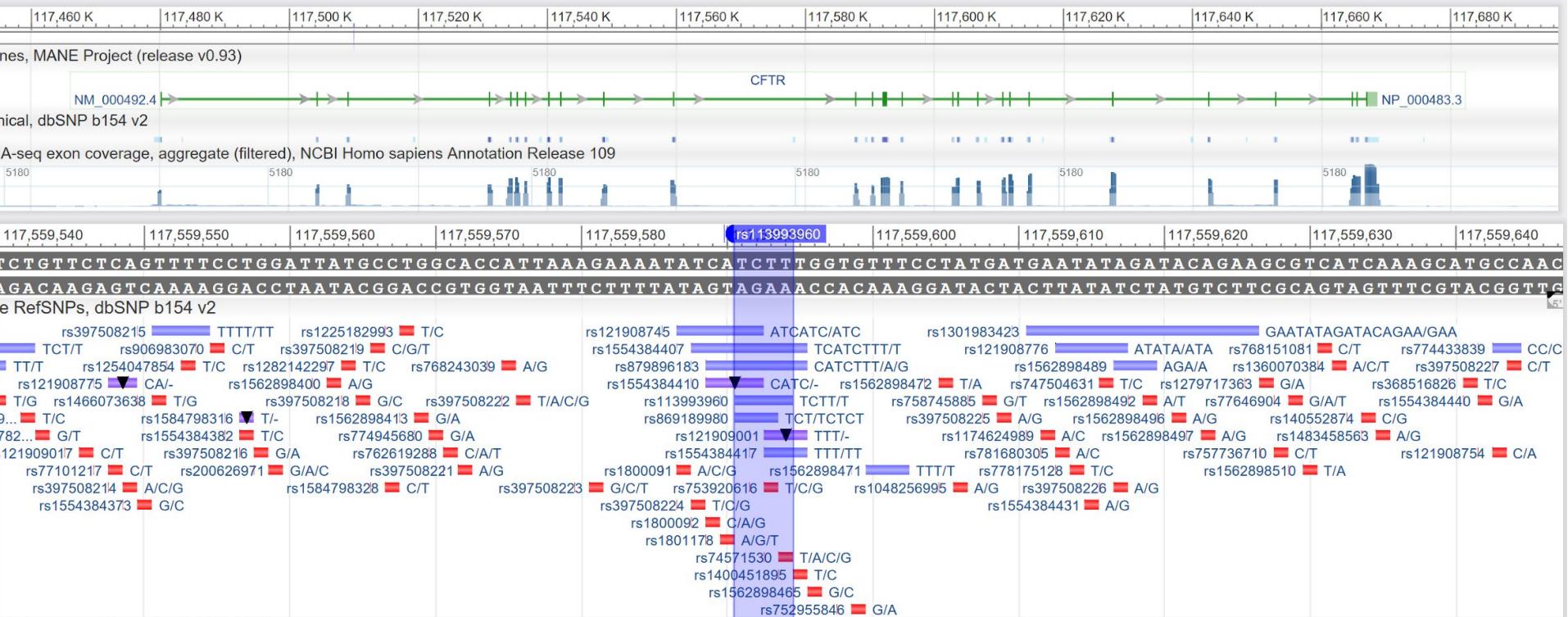



a

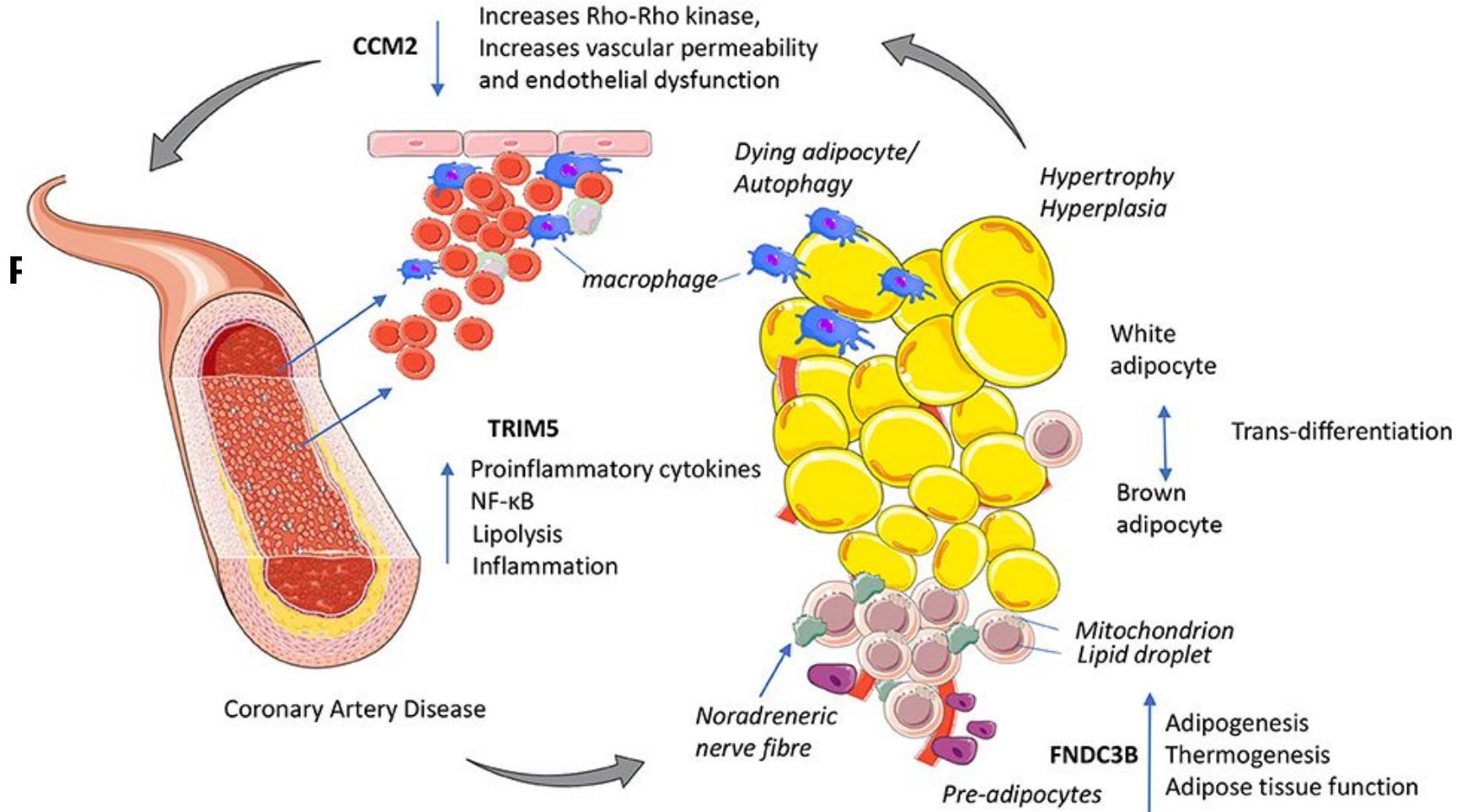
	CNV			Other SV (non-CNV)				Unresolved
SV class	Deletion	Duplication	Multiallelic CNV	Insertion	Inversion	Translocation	Complex SV	Breakends
Abbrev.	-DEL	-DUP	-MCNV	-INS	-INV	-CTX	-CPX	-BND
Ref.								
Example alternatives								
							(See Fig. 2)	Discarded



Cystic fibrosis

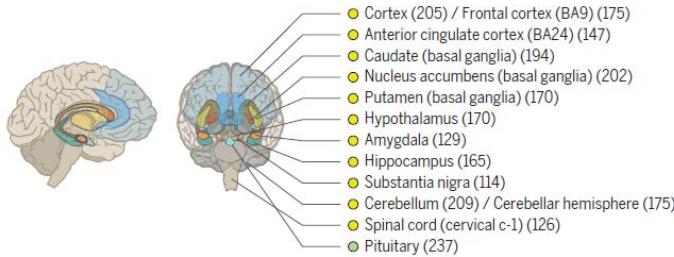


The *CFTR* gene (Chr 7), and rs113993960, the most common cause of CF



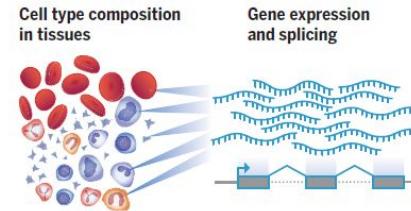
Dna Se

A



B

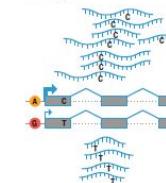
Cell type composition
in tissues



Gene expression
and splicing

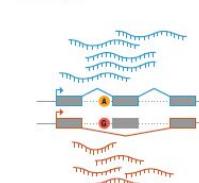
Expression quantitative
trait loci (eQTLs)

cis-eQTLs

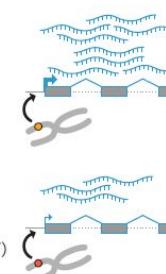


Splicing quantitative
trait loci (sQTLs)

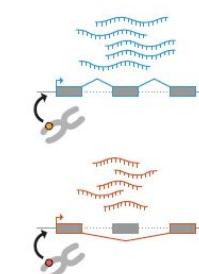
cis-sQTLs



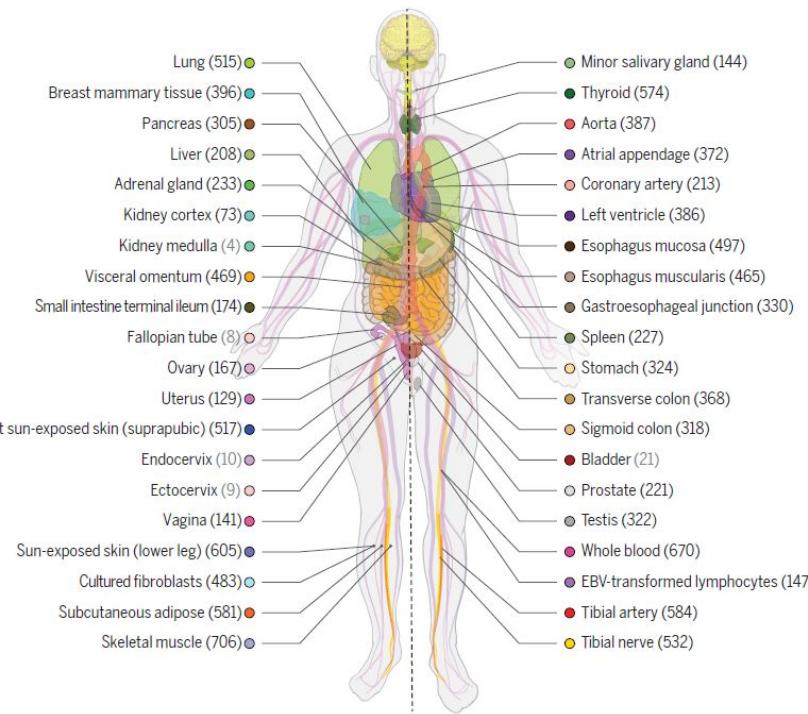
trans-eQTLs



trans-sQTLs



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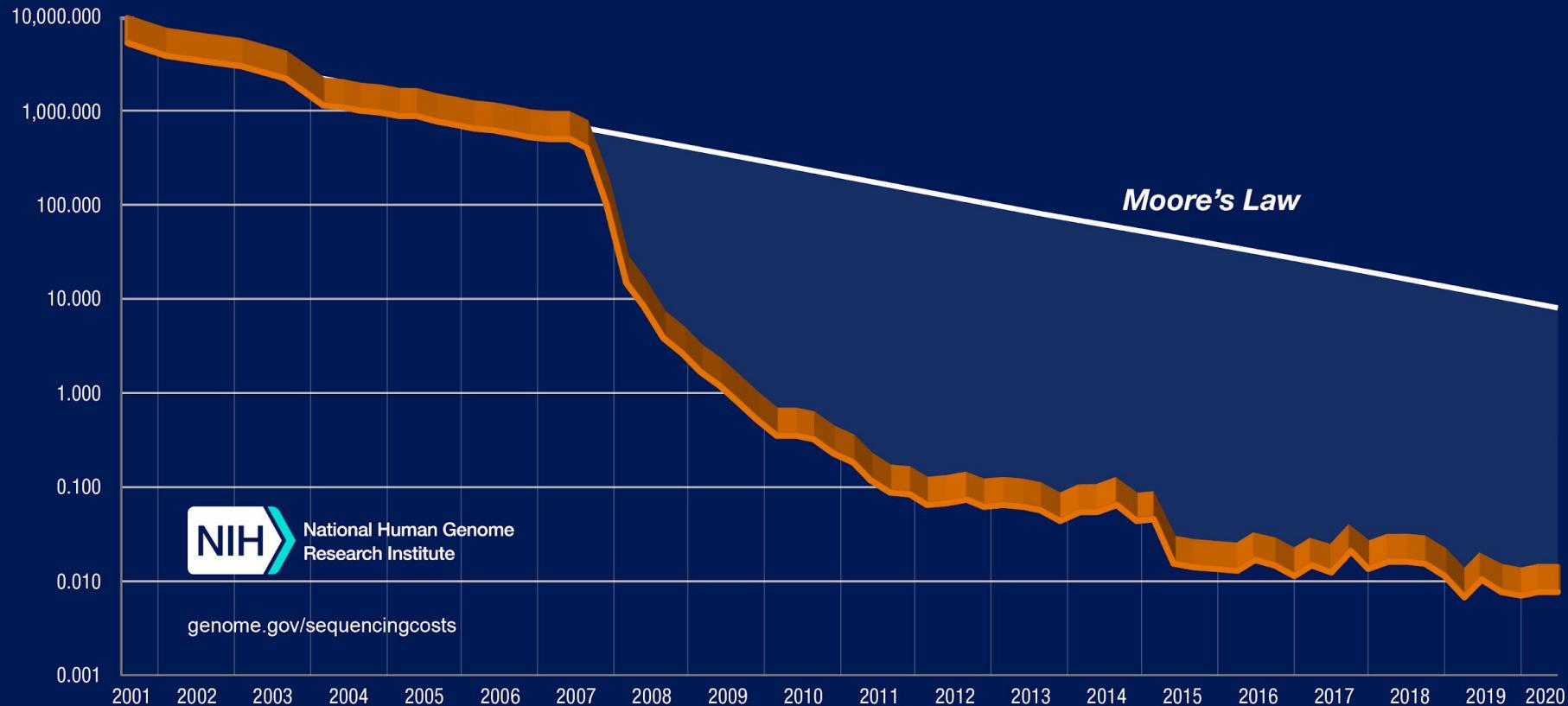


GTEX (v8)



National Human Genome
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Cost per Raw Megabase of DNA Sequence

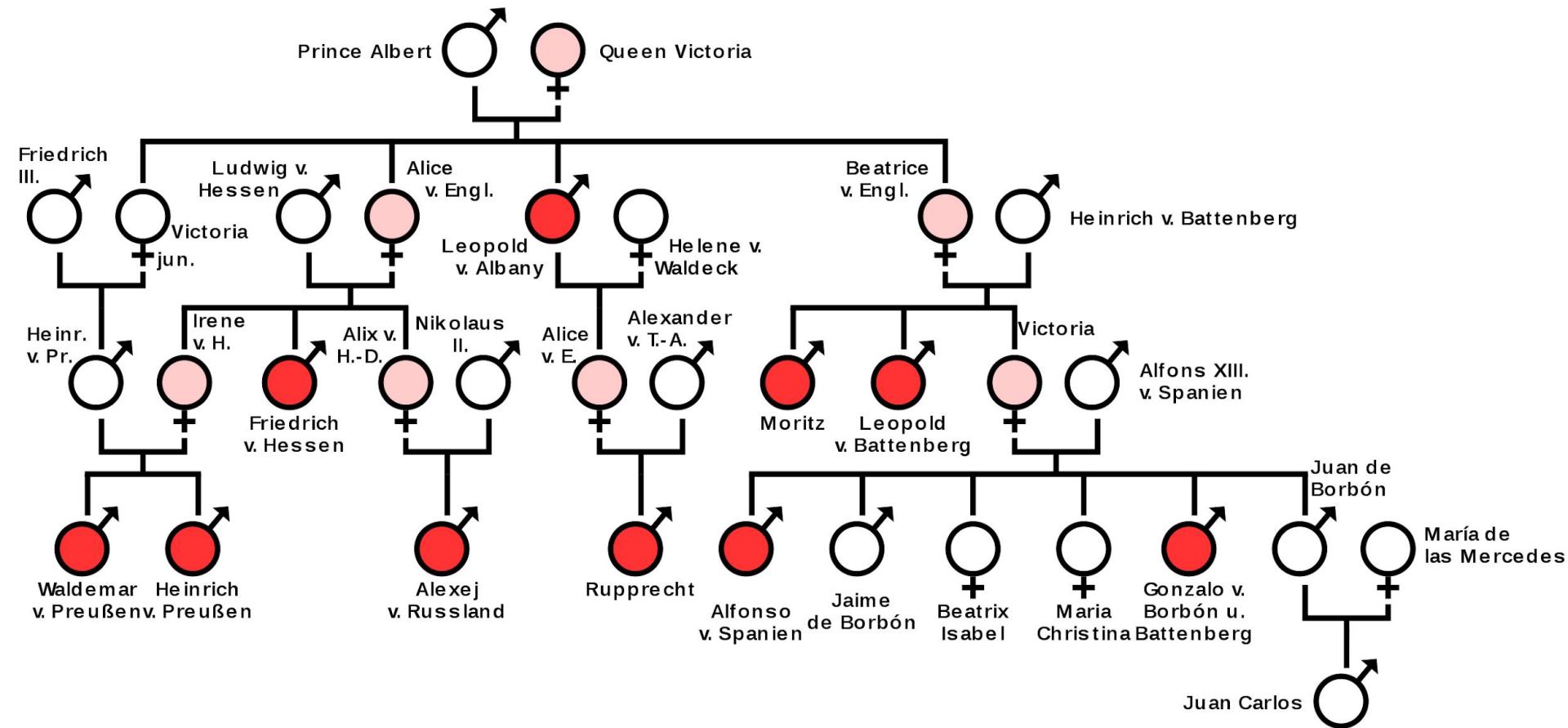
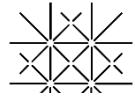


Cost per Human Genome



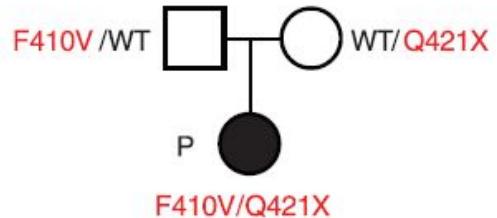


Haemophilia in the descendants of Queen Victoria

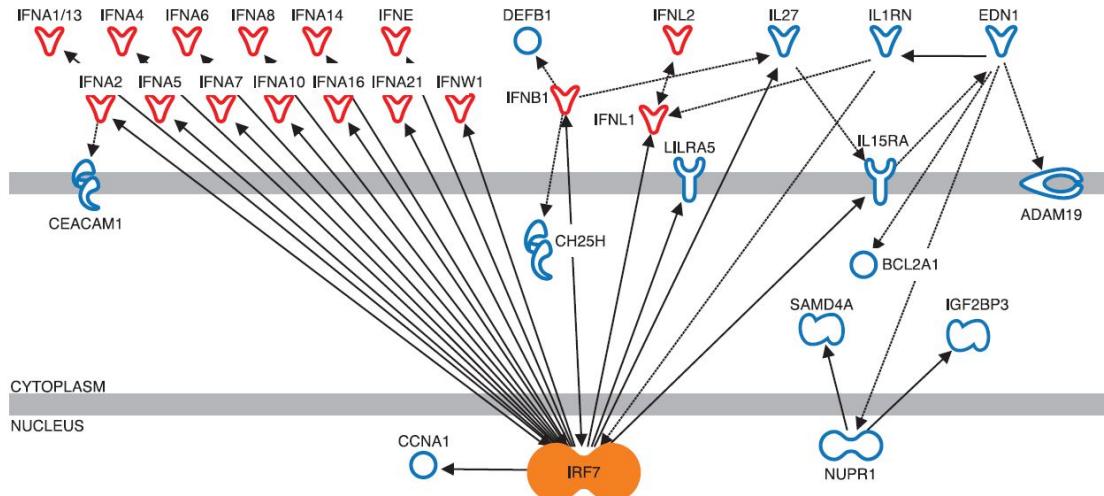
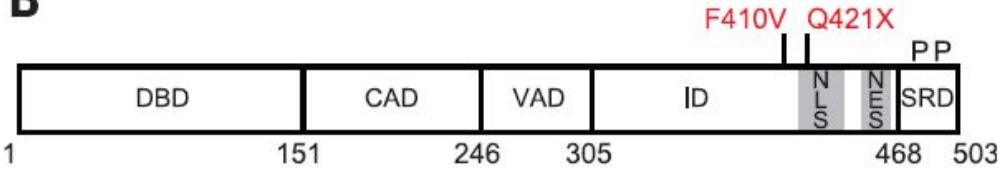


Life-threatening influenza infection in human IRF7 deficiency detected by trio sequencing

A



B



Exercise of *inference* (I)

The company *Fränzi and Friends* developed a new quick test at home for SARS-Cov-2 which is pending regulatory agency's review. The test has been shown to have a sensitivity of 99% and a specificity of 99%.

Suppose that Fred uses the test by *Fränzi and Friends* and the test was positive. Assume that 5% of the population is in fact infected. Was is your guess about the probability that Fred is indeed infected?

(Sensitivity is predicted true positive divided by all true positive; specificity is predicted true negative divided by all true negative).

Exercise of *inference* (I) - variants

The company *Fränzi and Friends* developed a new quick test at home for SARS-Cov-2 which is pending regulatory agency's review. When test with 100 SARS-Cov-2 patients, 99 report positive and one reports negative. When test with 100 healthy volunteers, 99 report negative and one reports positive.

Suppose that Fred uses the test by *Fränzi and Friends* and the test was positive. There are 30,000 people in the city where Fred lives; among them 1,500 are infected with SARS-Cov-2. What is the likelihood that Fred is truly infected given his positive test?

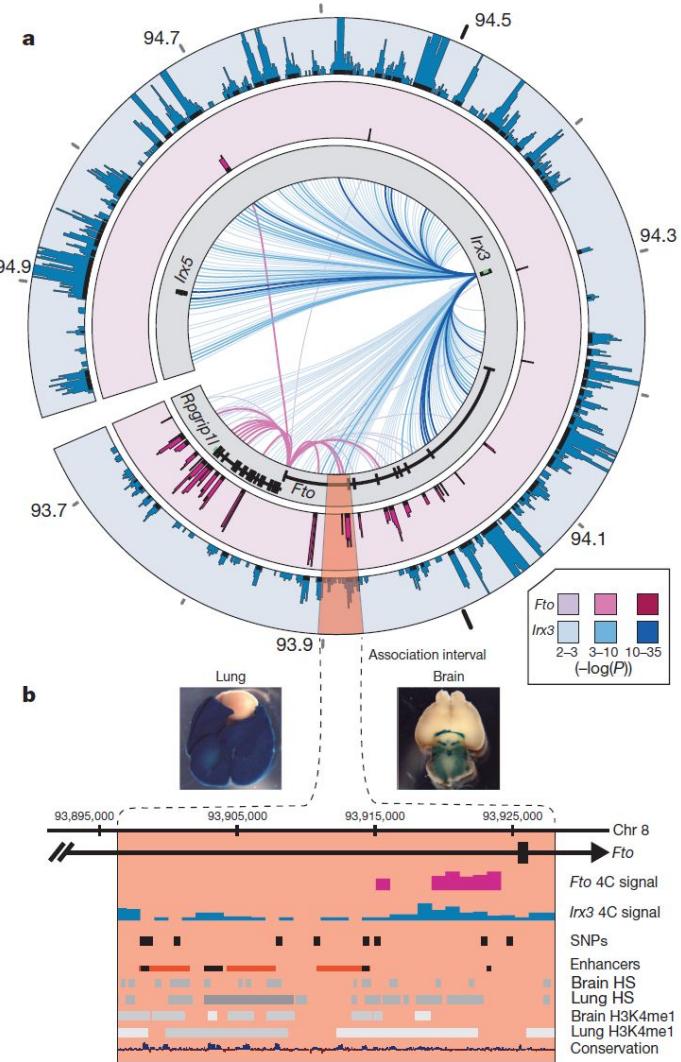
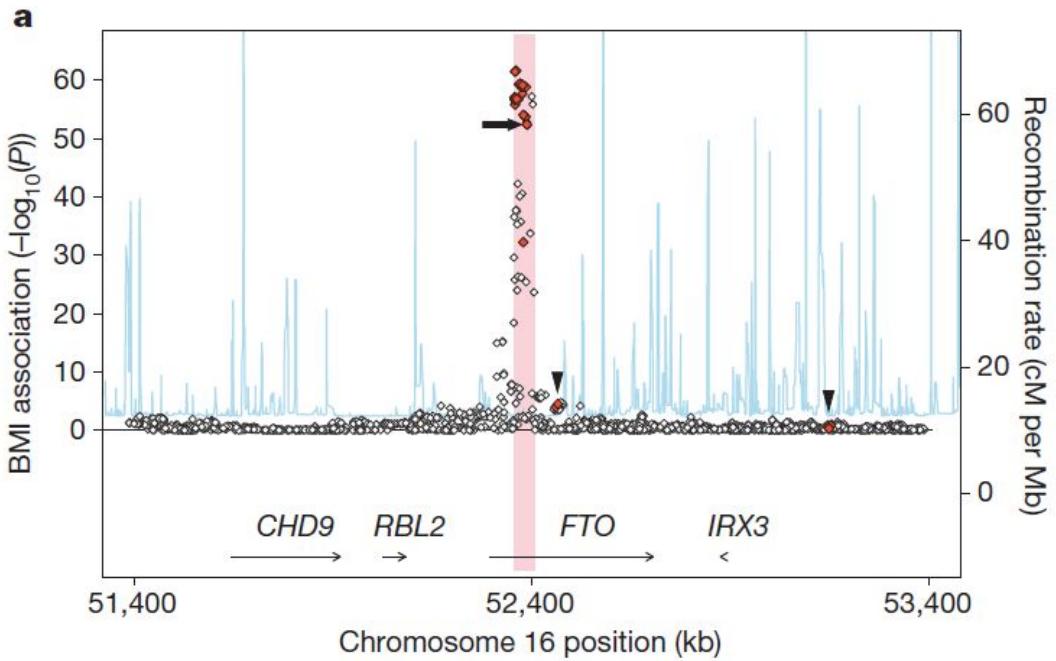
Exercise of *inference* (II)

Let's play a game! (The credit goes to David MacKay)

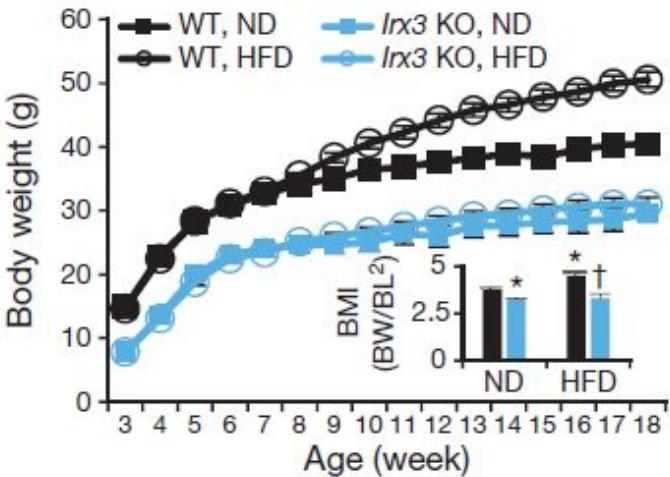
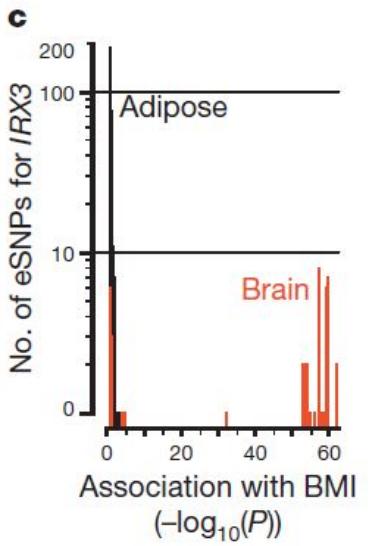
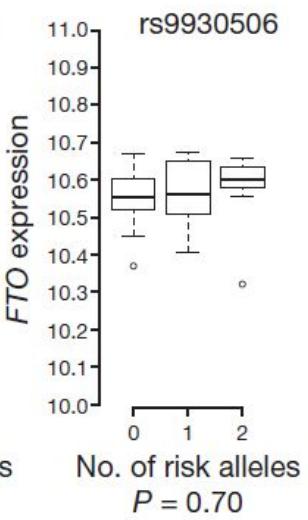
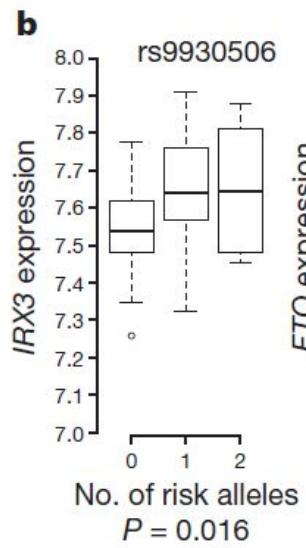
Exercise of *inference* (III)

- Cao and Moult (BMC Genomics, 2014) reported studied overlap between drug targets and GWAS hits.
- Use the data in the Table 1 of the paper ([cloned here](#)) to answer following the following two questions:
 - a. Assuming we know *nothing* about a gene (let's call it gene *WKN1*), what is the probability that the gene is a target for a disease listed here?
 - b. Assuming that we know nothing about another gene *WKN2* but that it is a GWAS hit for a disease, what is the probability that *WKN2* is a target for that disease?

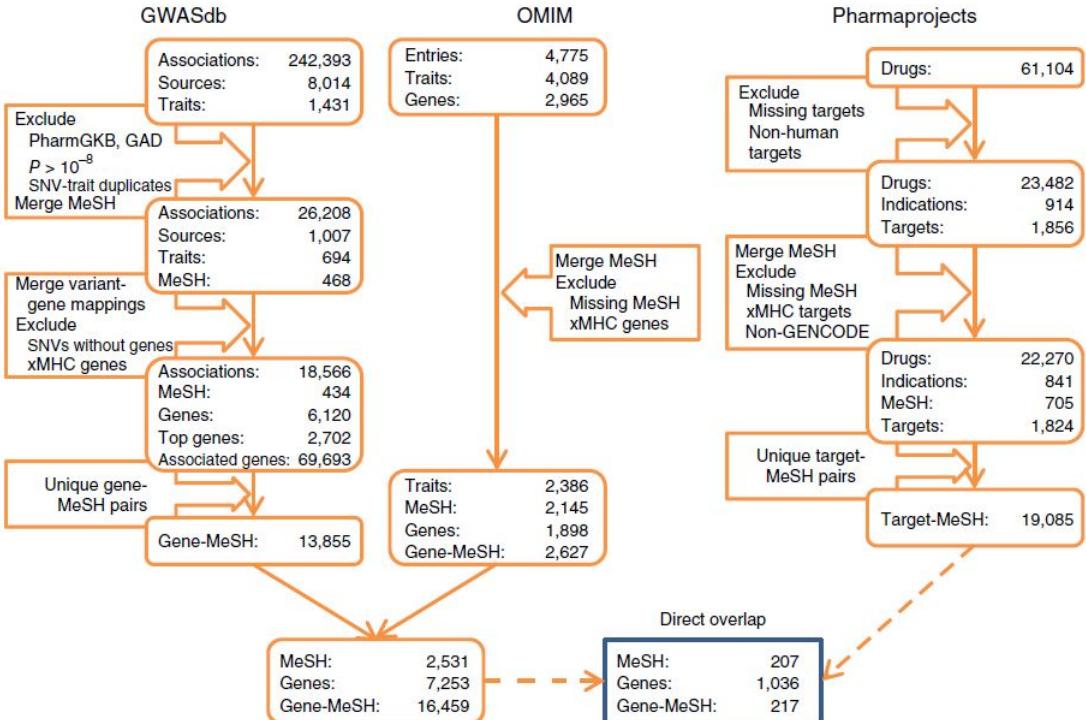
Is FTO a good target for obesity?



If at all, **IRX3** is a more probable target

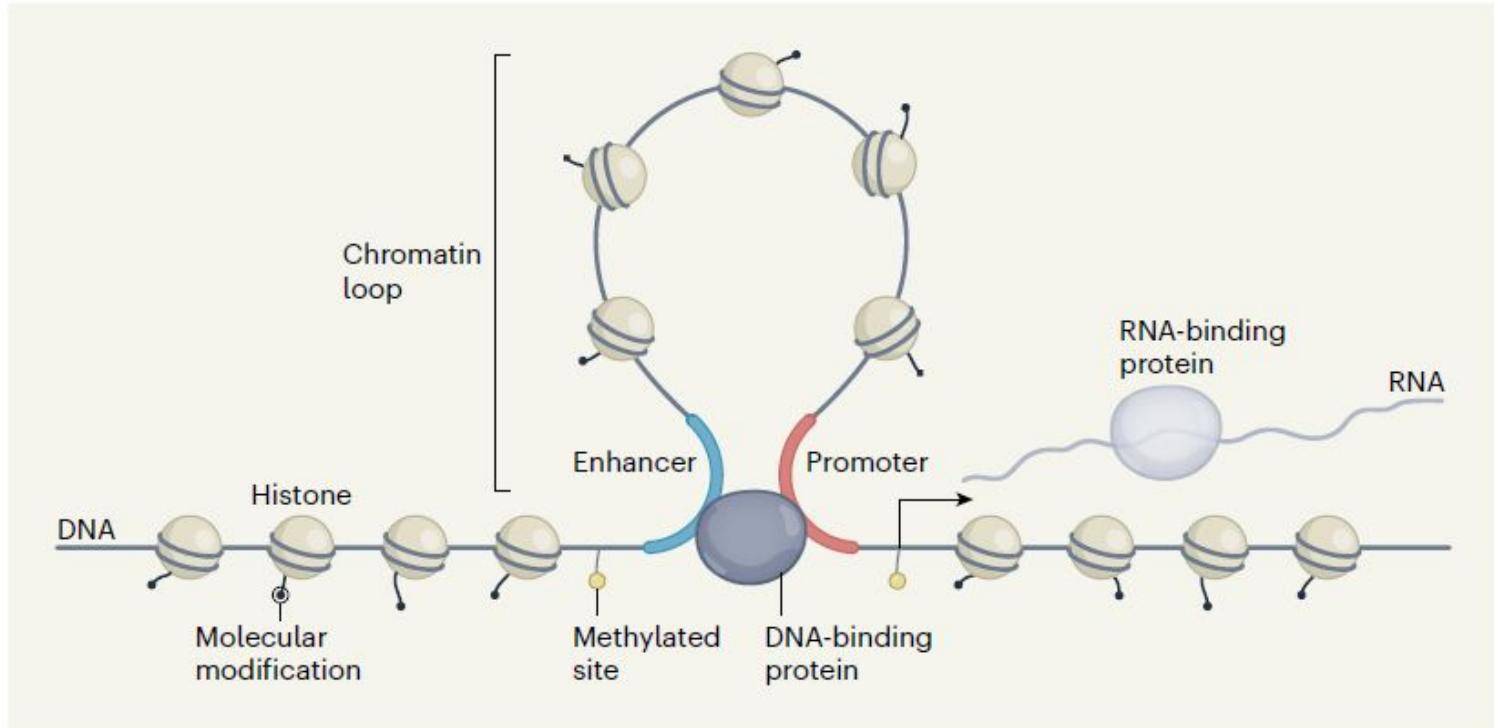


Impact by a factor of ~2 estimated by Nelson et al.

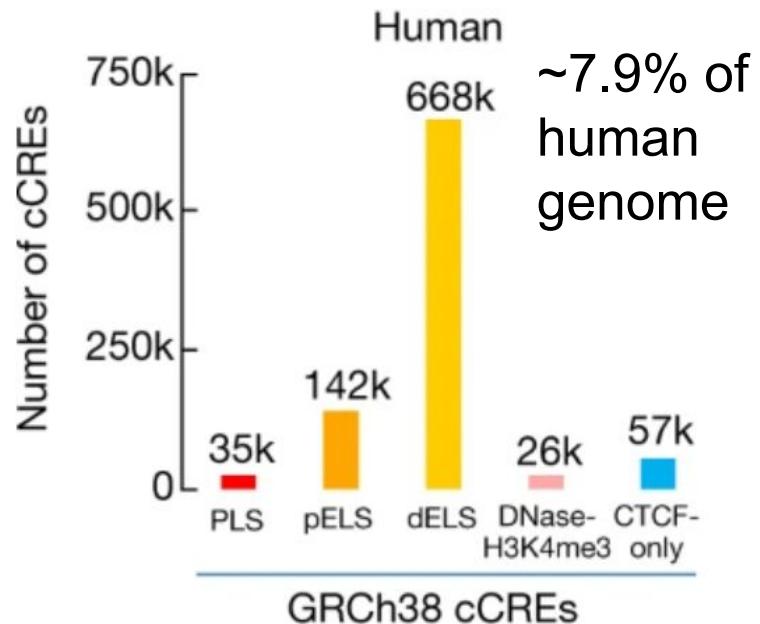
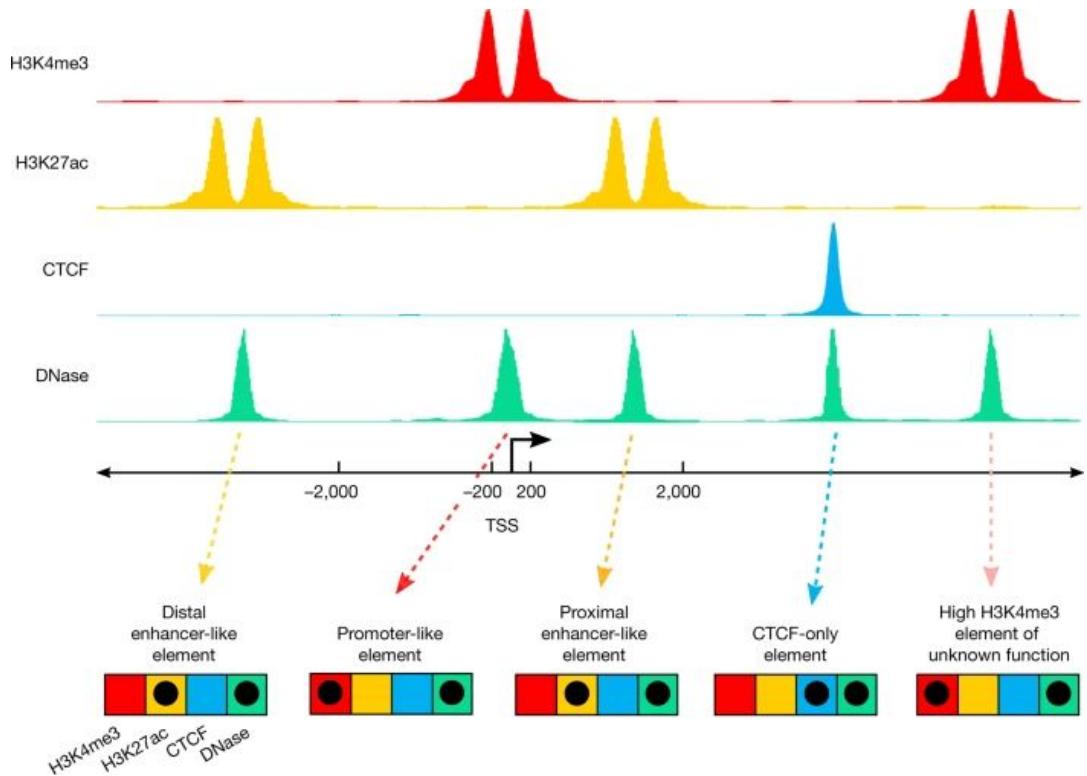


Disease \longleftrightarrow Gene \longleftrightarrow Drug

Much of the non-coding genome is junk, some is regulatory



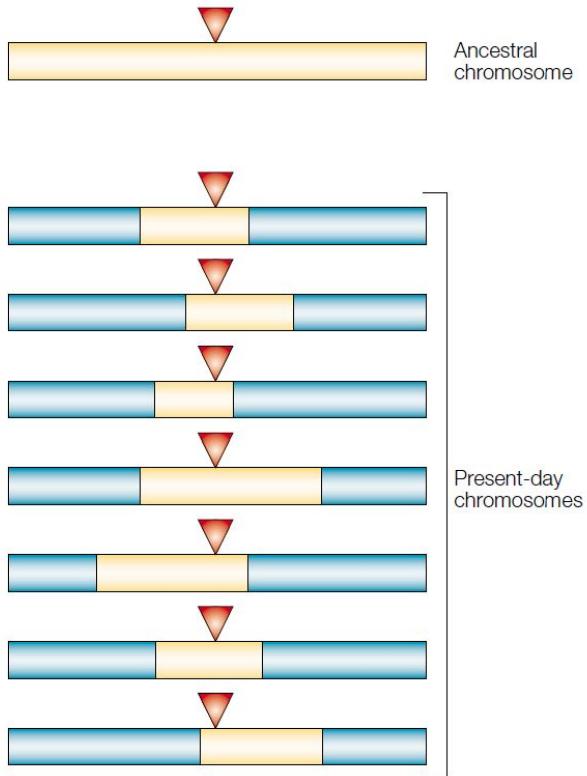
Candidate cis-regulatory elements (cCRE)



<https://screen.encodeproject.org/>

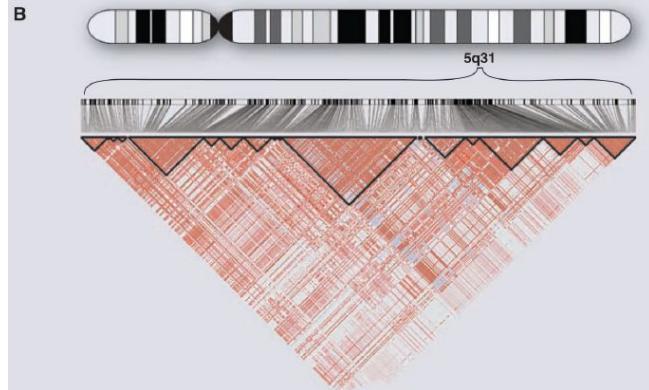
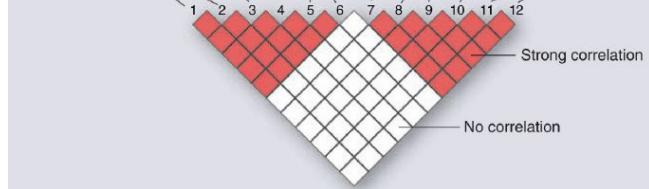
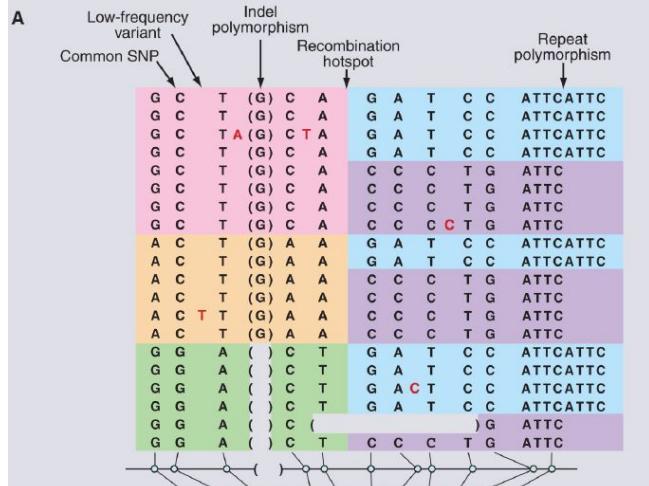
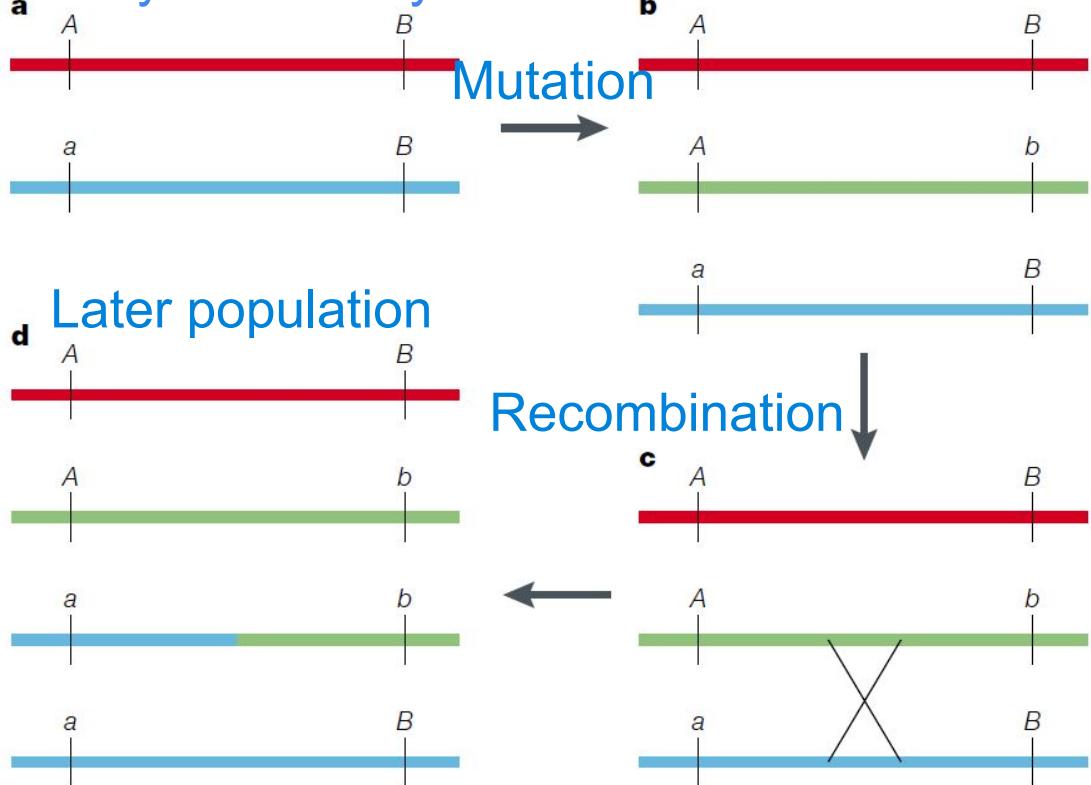
Linkage Disequilibrium in human genome

Particular alleles (single gene copies) at neighbouring loci tend to be co-inherited. For tightly linked loci, this might lead to associations between alleles in the population. This property is known as linkage disequilibrium (LD).

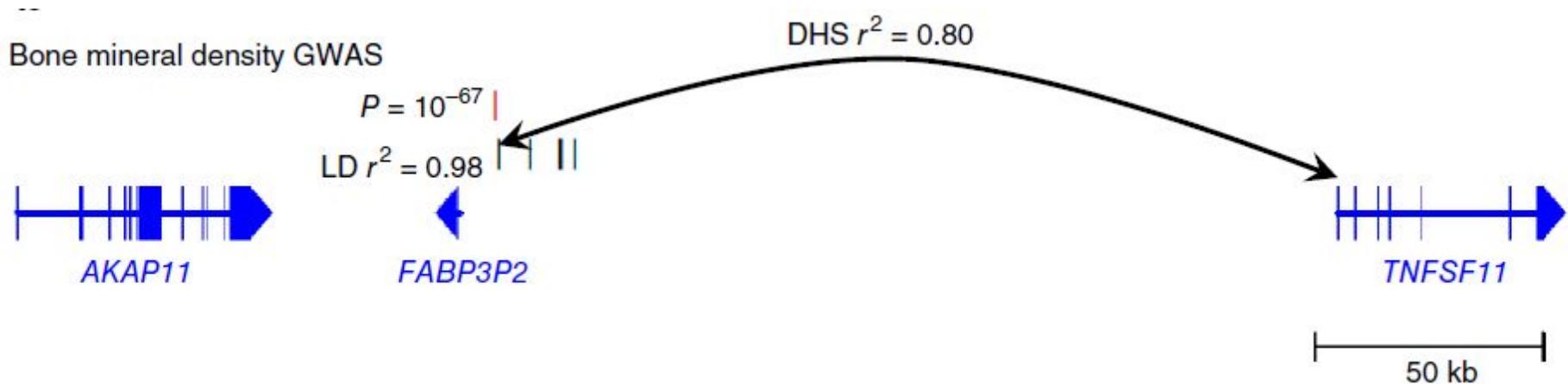


Population genetics helps with disease mapping

Early in ancestry



Correlation between DNase I hypersensitive (DHS) sites helps linking genetic variants with genes



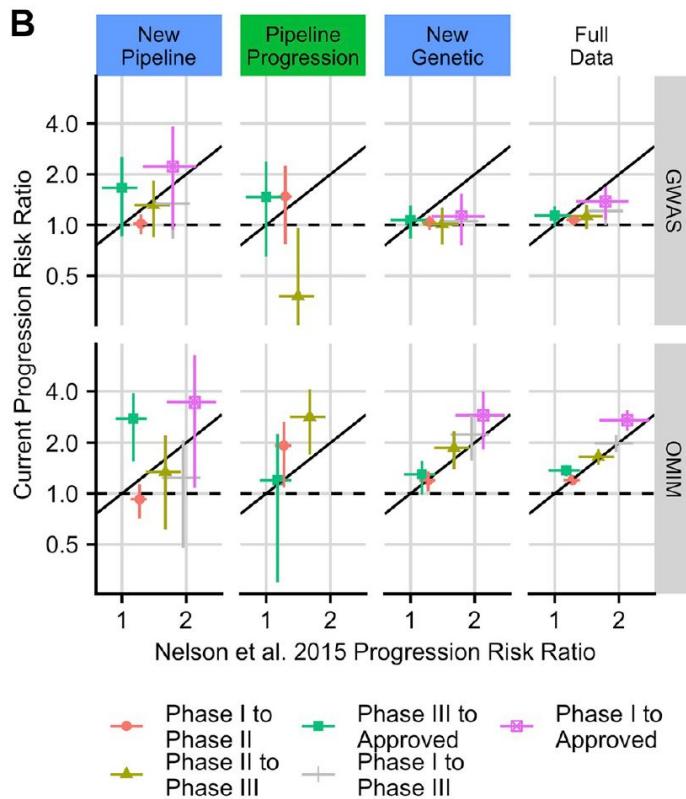
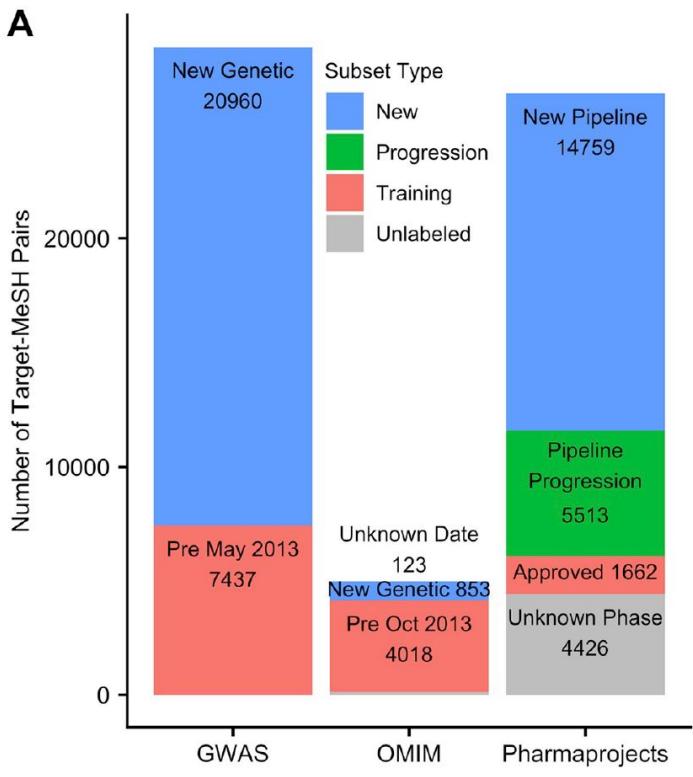
Nelson *et al.* inferred that genetic support offers an likelihood ratio ~2

Table 1 The relative value of genetic support for the probability that a target-indication pair progresses along the drug development pipeline, based on historical drug trial information

Progression	$p(\text{progress} \text{genetic support}) / (\text{progress} \text{no genetic support})$		
	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.

Follow-up study by King et al., 2019



Genes with *biologically understandable* genetic association are more likely to be good targets

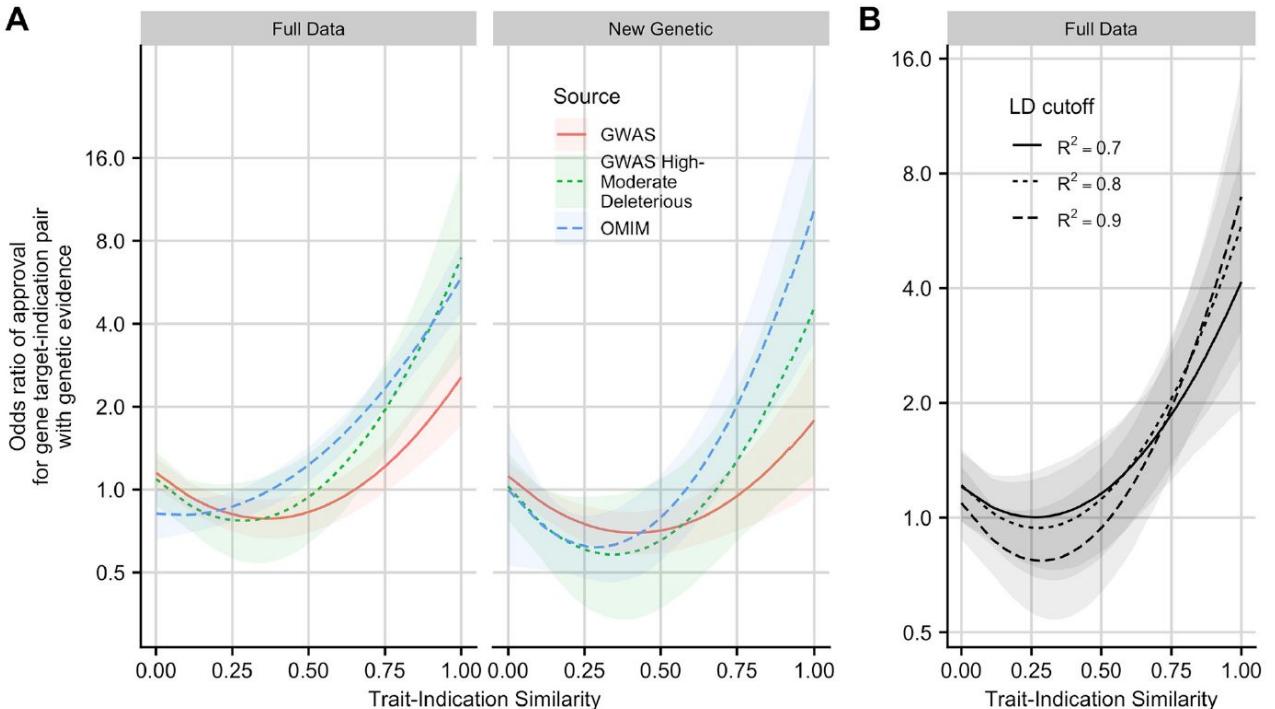


Fig 2. Estimated odds ratio of gene target-indication pair attaining approval, as a function of similarity between drug indication and the most similar trait associated with the target. A: Left: All genetic associations. Right: Only genetic associations reported after 2013 download. B: Effect of LD expansion threshold R^2 on the estimated approval odds ratio of a drug gene target-indication pair supported by a GWAS high-moderate deleterious variant. Posterior median and pointwise 95% credible interval from Bayesian logistic regression.

Discussion

What other evidences can we use to increase the likelihood that a gene is a good drug target?

GOT-IT recommendations for target-disease linkage

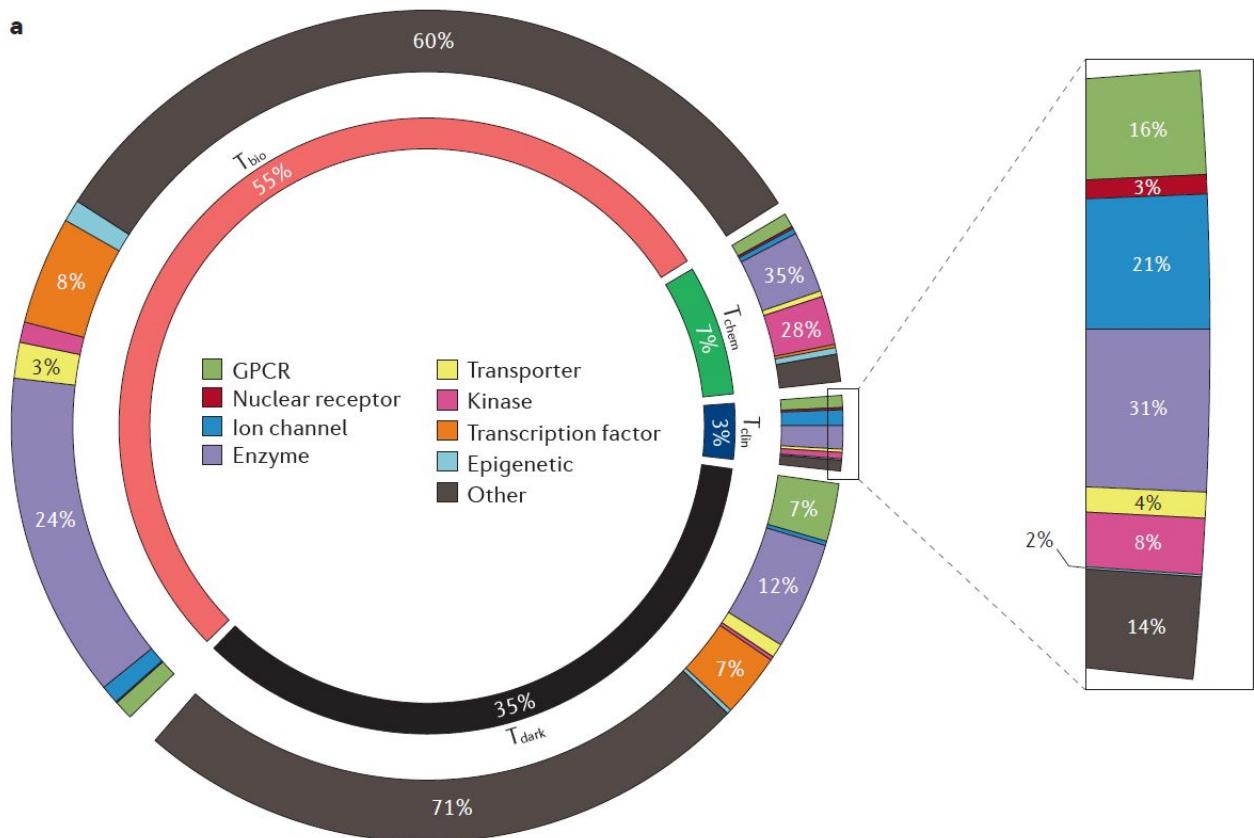
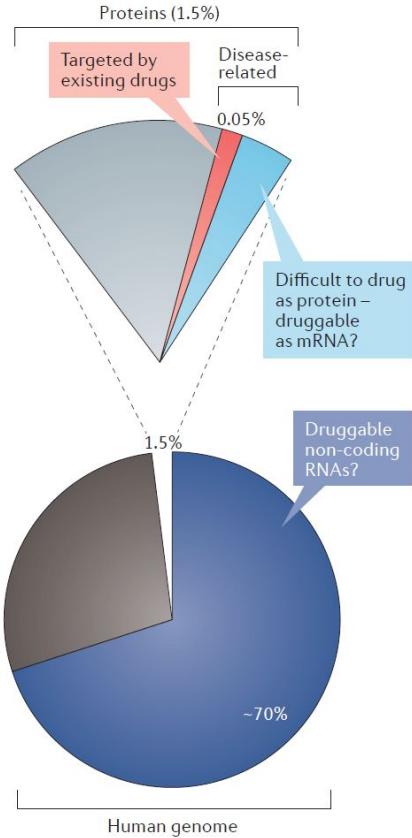
Assessment blocks



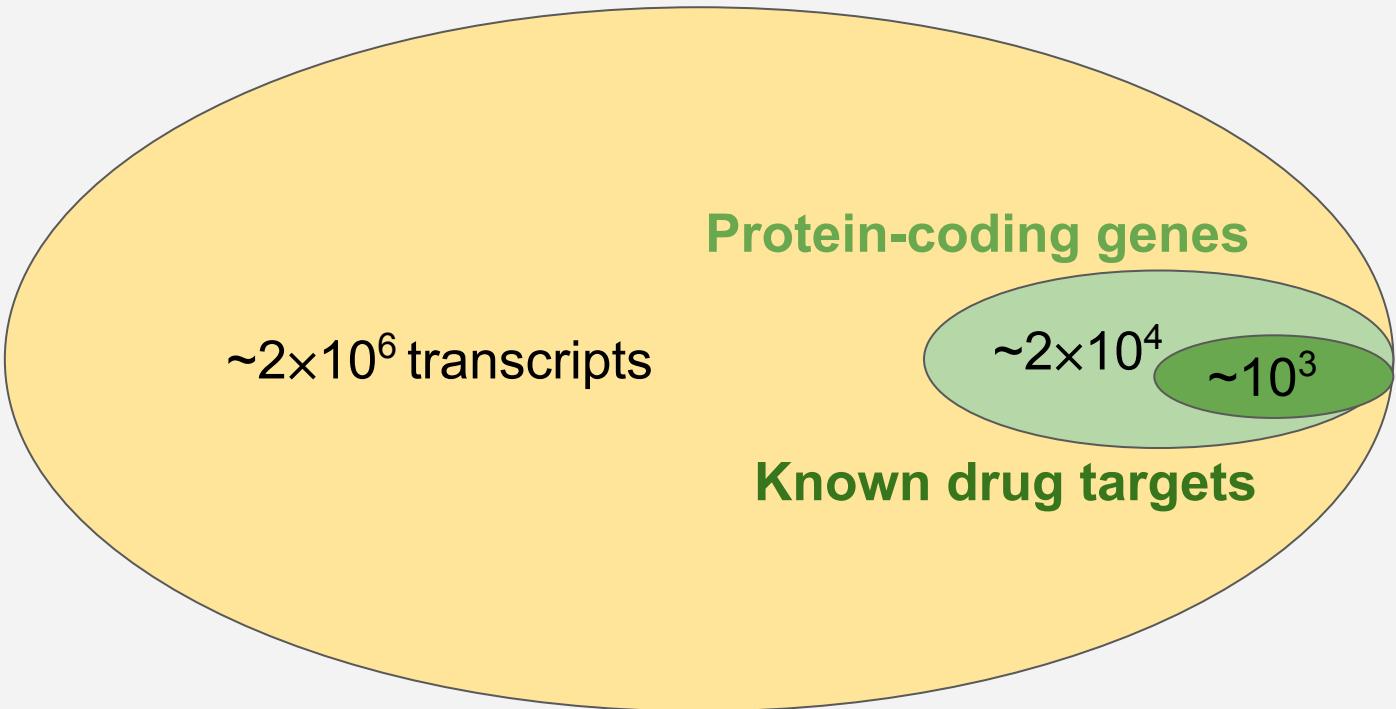
AB1: target–disease linkage (human targets)

1. Is the target perturbation a cause or consequence of the human disease process?
2. Is the therapeutic relevance (such as human connection) of models used sufficiently high for decision-making?
3. Is the target expression pattern known (that is, within the anticipated patient population)?
4. Is the target manipulation process clinically relevant?
5. Is the read-out used to detect target-dependent processes disease-relevant?
6. Is the stimulus used to activate or influence target-dependent processes disease-relevant?
7. Are the biological consequences of an observed effect size known?

Challenge #1: little experience for much of the genome

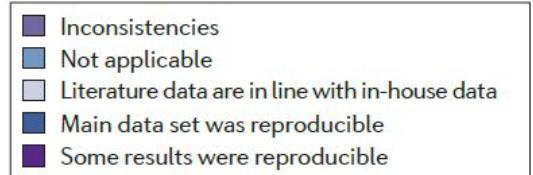
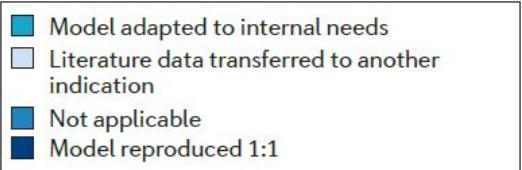
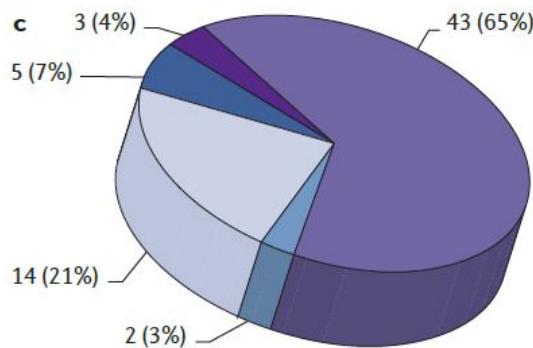
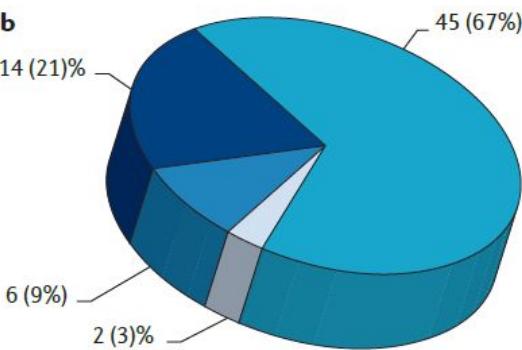
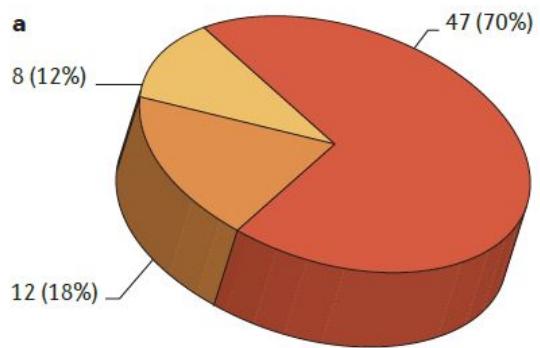


Protein, RNA, or DNA as target?



$\sim 3 \times 10^9$ DNA bases from maternal and paternal each

Challenge #2: Lack of reproducibility

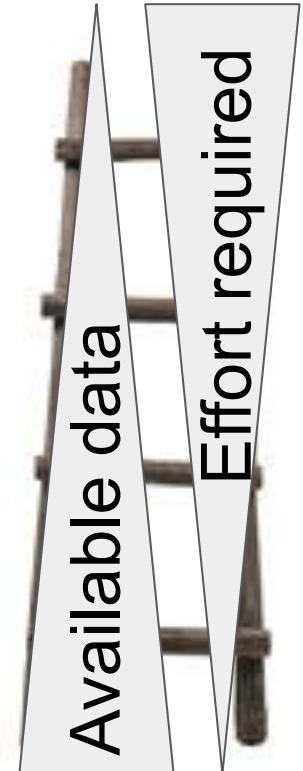


d

	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

Challenge #3: The Target Ladder

3. [Real-world test] What would happen if we inhibit the activity of the kinase domain in the *WKN3* gene in patients with Alzheimer's Disease?
2. [Intervention] What would happen to human cells or to a rat model if we inhibit the activity of the kinase domain in the *WKN3* gene?
1. [Association] What are the evolutionary conservation, sequence, expression profile, expression regulation patterns, ... of the *WKN3* gene?



Conclusions

- Genomics and genetics offer unprecedented opportunities and challenges for target identification and assessment;
- Target identification and assessment involves knowledge integration and experimental validation;
- A central task of mathematical and computational biology in drug discovery is to perform inference, i.e. using information to reduce uncertainty.

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